CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
CREOSOTE

Chemical Code # 171, Tolerance # 50436
SB 950 # 157

July 9, 1987
Updated 12/08/89, 9/14/90, 11/14/91, 1/18/95, 7/24/95, 3/18/96 and 1/9/98

I. DATA GAP STATUS

Chronic toxicity, rat:	Not required at this time[1]
Chronic toxicity, dog:	Not required at this time[1]
Oncogenicity, rat:	Not required at this time[1]
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, possible adverse effect
Teratology, rat:	No data gap, possible adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, possible adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, study not required at this time[2]
Neurotoxicity:	Not required at this time

[1] Document No. 50436-031 contains a "Notice of Intent to Suspend" from DPR to Koppers Industries, dated 5/23/96. That notice lists oncogenicity (mouse) as the sole outstanding animal study required by DPR under SB-950.

[2] The registrants had requested a waiver for this study category, agreeing that creosote is mutagenic. See memorandum of March 18, 1996, from J. Gee asking for concurrence from OEHHA for a waiver on DNA damage studies. On 11/4/96, the staff of OEHHA wrote a memorandum to Jean-Marie Peltier, Chief Deputy Director at DPR, concurring with the request by the registrants for a waiver for further genotoxicity studies.

Note, Toxicology one-liners are attached. 1/9/98 revision by Aldous.

In the one-liners below:
** indicates acceptable study
Bold face indicates possible adverse effect

These pages contain summaries only. Individual worksheets may identify additional effects. Records below were reconciled with the DPR library printout of 1/6/98. All relevant data through Record No. 153463 (Document No. 50436-031) have been considered in the 1/9/98 Summary.

INTRODUCTION

"Creosote", as it applies to the pesticide industry (chiefly as a wood preservative), is a generic term for comparatively high boiling components obtained from the coking process of fossil fuels. In addition to containing a mixture of polycyclic aromatics, "creosote" contains a number of acidic, basic, and neutral components. Commercial "creosote" may vary substantially in composition depending on source materials, coking processes, and fractions selected. The most recent studies have utilized industrial composite blends, to be as representative as possible of industrial creosotes. C. Aldous, 7/9/87, 12/8/89, and 1/6/98.

A 1985 IARC monograph on creosote and related materials cites data on animals (predominantly mice) and on humans exposed occupationally (see Document No. 50436-021, Record No.132720 at the end of the “Oncogenicity, Mouse” section of this Summary of Toxicology Data). As noted below, the monograph concluded that there is "sufficient evidence" that coal-tar is carcinogenic in humans (causal association with skin cancer). Further, there is 'limited evidence' that coal-tar-derived creosotes are carcinogenic in humans".

U.S. EPA has made extensive evaluations on major wood preservatives, including creosote, during the last two decades. EPA determined in its 1988 publication (Guidance for the Reregistration of Pesticide Products Containing Coal Tar/Creosote as the Active Ingredient) that a mouse skin painting study would be necessary and sufficient for completing long-term exposure effects evaluation, complementing the existing database in effects of occupational exposure and a sizeable number of mouse dermal exposure studies. DPR has concurred with that determination. Since a valid 6-month dermal oncogenicity study in mice has been reviewed, the other chronic study requirements are considered filled at this time. Aldous, 1/9/98.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

CHRONIC TOXICITY, RAT
Not required at this time

CHRONIC TOXICITY, DOG
Not required at this time

ONCOGENICITY, RAT
Not required at this time

ONCOGENICITY, MOUSE

****50436-031 153463** Naas, D. J., “A 6-month dermal oncogenicity study of creosote in mice”, WIL Research Laboratories, Inc. (Project No. 100005), 3/7/97. Groups of 30 male Crl:CD-1®(ICR)BR mice were dosed in an initiation/promotion study (2 wk initiation, 2 wk rest period, and 26 wk promotion), with materials applied to clipped dorsal skin. Acetone was the carrier and negative control, DMBA (= 9,10-dimethyl-1,2-benzanthracene) was used as the positive initiator, and TPA (12-0-tetradecanoylphorbol-13-acetate) was the positive promotor. Creosote (“North American P1/P13 Creosote CTM”, Lot #P1/13-009-A) was used at 3 dose levels, either to

evaluate initiation potential (2 weeks of applications, 5 times/week) or promotion potential (applications twice weekly for 26 weeks). Creosote treatments per application were 500 µg/mouse (low dose), 25 mg/mouse (medium dose), or 56 mg/mouse (high dose). Mean mouse body weights were close to 40 g in all groups. Sustained treatment with creosote at the higher two dose levels resulted in 3-6 deaths/group, presumably due to skin damage (erythema, fissuring, eschar, exfoliation) with associated infection and general poor condition. Only lesions of the treatment site and other skin lesions were evaluated for histopathology. Negative control mice had no tumors, and positive controls were functional. Common tumors in positive control and creosote groups were benign papillomas and keratoacanthomas, and malignant tumors such as squamous cell carcinomas (common at higher dose levels) and basal cell carcinomas (uncommon and restricted to higher dose treatments). When creosote was used as an initiator with TPA for promotion, there was no difference between dose levels in numbers of benign tumors (24-27 mice/group with papillomas, 4-7 mice/group with keratoacanthomas), but malignant tumors were limited to 2/group (squamous cell carcinomas) in the higher two creosote groups. When creosote was used as promotor in DMBA-initiated mice, the low dose of creosote yielded only two tumors (papillomas), whereas the medium and high dose creosote groups yielded 20-22 papillomas, 10 to 12 keratoacanthomas, 19-23 squamous cell carcinomas, plus 1 and 2 basal cell carcinomas, respectively. When the high dose creosote level was used for both initiation and promotion phases, tumor yields were 16 papillomas, 4 keratoacanthomas, 26 squamous cell carcinomas, and 2 basal cell carcinomas; indicating that creosote is a “complete” carcinogen. Although creosote was shown to be an effective initiator at all dose levels when coupled with a powerful promotor, the most relevant outcome from this study was a clear dose-response when creosote was evaluated as a promotor. This specialized study fills the oncogenicity data gap, and no further chronic studies are requested at this time. Aldous, 1/8/98.

50436-026 142319 Protocol for the 6-month dermal mouse oncogenicity study above. Comments were sent to registrants by J. Gee, 11/17/95.

50436-028 Records 144580-144585 Publications used to support the amounts of DMBA to be used in the mouse skin painting study. See 50436-026 142319 above. (Gee, 2/26/96)

50436-012 55548, "The carcinogenic activity of some petroleum fractions and extracts: Comparative results in tests on mice repeated after an interval of eighteen months", (Cancer Research Laboratory), The Medical School, The University of Birmingham (England), 1944-1946). Creosote oil applied to a 1-1/2 cm diameter area of the interscapular area after hair removal of 50 albino white mice twice weekly for 25 weeks; oncogenicity reported; increase in incidence of papillomas and carcinomas at location of application. unacceptable; not upgradeable (Not standard chronic study, but useful information) (Green, C. Aldous 7/7/87).

50436-012 55549, "Experimental Carcinogenicity of Coal-Tar Fractions: The Carcinogenicity of Creosote Oils" (Dept. of Occupational Health, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, published 1957). Blended creosote oil at 20 or 80% dilution in toluene or light (low distillation range) creosote oil at 50% dilution; 1 drop of solution applied three times/week to shaved interscapular skin of C57L mice. 10 or 11 male/group and 8 or 9 female/group; most tests done in female mice and skin treatment was repeated for the life span of the animals or until development of a papilloma; adverse effect reported (tumor development in blended creosote mixtures with induction times intermediate between those of 0.05 and 0.25% benzo[a]pyrene (BP). Also, "light" creosote fraction induced local papillomas at frequency comparable to 0.05% BP); unacceptable; not upgradeable; (not standard study, but useful information) (Green, C. Aldous 7/7/87).

50436-012 55550, "A study of the Chemical Constitution and Carcinogenic Action of Creosote Oil, 1,2" (Division of Oncology, The Chicago Medical School, Chicago, Ill, Journal of the National Cancer Institute, Vol. 18, No. 5, May 1957), Creosote either undiluted, as 10% solution, or 2% basic fraction in acetone with a single dermal DMBA pre-treatment, and one undiluted creosote group without DMBA pre-treatment to groups of 30 Swiss female mice. An additional control group of 50 females received only DMBA pre-treatment. All treatments painted on the clipped interscapular skin twice weekly for 70 weeks; Carcinogenicity of undiluted creosote and some possible augmentation of DMBA pretreatment reported; Unacceptable, not upgradeable (Not standard study, but useful information) (Green, C. Aldous 7/7/87).

50436-012 55551, "The carcinogenicity of creosote oil: Its role in the induction of skin tumors in mice" (McArdle Memorial Laboratory), University of Wisconsin, Madison, Cancer Research, Vol. 18, November, 1958). Groups of 30 female mice of the Sutter strain were treated as follows: Initial treatments were single applications to the shaved mid-dorsal skin of 75 ug DMBA, 4-week application of creosote, or no initial treatment. Secondary treatments for DMBA-pretreated mice were continuous treatments of benzene, creosote, or croton oil. Creosote pretreated mice received either no secondary treatment or croton oil. Non-pretreated mice received secondary treatments with creosote or croton oil. Oncogenicity of creosote was demonstrated, however possible promoter activity could not be demonstrated under conditions of study (DMBA pretreatment plus continuous creosote treatment was not significantly different in tumor induction from continuous creosote treatment alone); Unacceptable, not upgradeable (Not a standard study, but useful information.) (Green, C. Aldous 7/7/87).

50436-012 55552, "The carcinogenicity of creosote oil: The induction of lung tumors in mice" (McArdle Memorial Laboratory, Medical School, University of Wisconsin, Madison, Cancer Research, Vol. 18, November 1958, pp 1176-1178). Creosote oil undiluted at 1 drop (25 ul) applied to the skin of the backs of Sutter-derived mice twice weekly for up to six months. Another group of mice were maintained in creosote-treated wooden cages for five months in addition to creosote skin application. Controls were untreated. A second experiment involved a shorter duration of creosote treatment (4 weeks). Corresponding controls received croton oil or benzene. Skin and lung tumors were reported in the groups of mice treated with creosote for 5-6 months, and numbers of lung adenomas were markedly higher in mice exposed both via creosote-treated cages and by dermal application; The second experiment found measurable increases in lung tumors in creosote-treated mice compared to controls, but no skin tumors were seen. unacceptable, not upgradeable (major variance from guidelines, but useful data) (Green, C. Aldous 7/7/87).

50436-012 55553, "Studies in carcinogenesis. XII. Effect of the basic fraction of creosote oil on the production of tumors in mice by chemical carcinogens" (U.S. Public Health Service, Office of Cancer Investigations, Wolcott Gibbs Memorial Laboratory, Harvard University, Cambridge, MA, Journal of the National Cancer Institute) (Pub. about 1940). A 1% or 2% **basic fraction of creosote** in benzene with/without benzpyrene (BP) was painted on the skin of Strain A mice 3 times/week for 1 year (or until high yield of tumors was obtained). Other mice received the same basic fraction in lard with/without BP as a single or repeated subcutaneous injection; tumor promotion was reported; such promotion was only observed only when BP concentrations were low on skin (0.05 or 0.02%) or when only a single subcutaneous injection of 0.1 mg BP in conjunction with creosote basic fraction was given. (Higher doses of BP masked the promotion effects of basic fraction). Unacceptable; not upgradeable, [not standard study] but useful information (H. Green, C. Aldous, 7/8/87).

50436-012 55554, "Studies in Carcinogenesis. IX. Development of skin tumors in mice painted with 3:4-benzpyrene and creosote oil fractions" (Samuel Cabot, et al., Laboratory of Samuel Cabot, Inc., Boston, Mass., and U.S. Public Health Service Cancer Investigations, Wolcott Gibbs, Memorial Laboratory, Harvard University, Cambridge, Mass., Pub. ca. 1940). Creosote subfractions in benzene with/without 0.2 or 0.05% benzpyrene (BP) applied to the clipped backs of female albino market mice, 20/group, 114 treatments/38 weeks; tumor promotion reported with 1% basic fraction and to a lesser extent with 25% neutral fraction and steam distillate of neutral fraction; Tumor production due to 0.05 or 0.2% BP apparently retarded by phenolic fraction, neutral residue and neutral distillate, and by the unfractionated creosote. **Unacceptable; not upgradeable** (but useful information). (Green, C. Aldous 7/8/87).

50436-021 132720 "Polynuclear Aromatic Compounds, Part 4, Bitumens, Coal-tars and Derived Products, Shale-oils and Soots". One of the WHO "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans", Vol. 35, January 1985. Brief abstracts of several mouse studies were presented. Creosotes commonly elicited skin papillomas and carcinomas. Human case reports relating to creosotes suggested increased cancers of the skin and scrotum. Evidently the sizes of exposed populations to coal-tars and pitches were larger than those exposed to creosotes, allowing for more comprehensive analyses, and in some cases indicating a larger variety of suspected cancer effects than for creosotes. The monograph summary concluded that there is "sufficient evidence" that coal-tar is carcinogenic in humans (causal association with skin cancer). Further, there is 'limited evidence' that coal-tar-derived creosotes are carcinogenic in humans". Aldous, 1/11/95 (no DPR worksheet: no reviewable "studies" in the text of the monograph).

REPRODUCTION, RAT

****50436-025 138222** York, R. G., "Two generation reproduction/fertility study in rats", IRDC Lab. Project ID #672-006, 3/13/95. Charles River Crl:CD VAF® rats, 26/sex/group, were dosed with "North American P1/P13 Creosote CTM" (a representative commercial composite) in corn oil vehicle by daily gavage at 0, 25, 75, or 150 mg/kg/day. This was a typical reproduction study with 1 litter per generation, unusual in that pre-mating period dosing of F1 rats was delayed until 35 days of age, and the pre-mating treatment phase lasted about 17 weeks. Parental effects NOEL < 25 mg/kg/day (decrement in pre-mating body weights, F1 females). Common parental effects at 75 to 150 mg/kg/day included minor body weight decrements and clinical signs of increased salivation and anogenital staining. At 150 mg/kg/day, body weight decrements were marked, especially for F1 males. Reproductive effects NOEL < 25 mg/kg/day (very low fertility and pregnancy indices, without dose-response, in the F1 parental generation). At 75 to 150 mg/kg/day there was a decrease in live pups per litter. This was associated with increases in stillborn pups at 75 mg/kg/day, yet a much greater increase in stillborn pups at 150 mg/kg/day did not fully account for the dramatic drop in live pups born at that dose. Gestation length was slightly protracted at 150 mg/kg/day. Developmental toxicity NOEL = 25 mg/kg/day (modest pup b.w. decrements during lactation). Pup survival at 150 mg/kg/day was reduced in the F0 mating trial. There was a notable incidence of microphthalmia among F1 pups at 150 mg/kg/day (5 pups from 2 litters). Study is **acceptable**, with "**possible adverse effects**" (low pregnancy indices at all dose levels in F1 mating trial, decreased live pups/litter, at least partially due to stillborn pups). C. Aldous, 7/20/95.

50436-017 115556 Protocol for a reproduction study in rats.

TERATOGENICITY, RAT

****50436-024 138221** York, R., "Developmental toxicity study in rats", IRDC Lab ID 671-020, 3/10/95. Thirty Crl:CD VAF® female rats per group were dosed by gavage with 0, 25, 50, or 175 mg/kg/day creosote (a composite mixture designated "North American P1/P13 Creosote CTM") during days 6-15 p.c. Maternal NOEL = 25 mg/kg/day (food consumption decrements during the latter part of the dosing period). Developmental NOEL = 25 mg/kg/day (overall increase in malformations, most notably microphthalmia/anophthalmia). There was an increase in early resorptions at 175 mg/kg/day, partially attributable to an increase in total litter losses in that group. The increased malformations and the increased resorptions are **"possible adverse effects"**. Study is **Acceptable**. C. Aldous, 7/24/95.

TERATOGENICITY, RABBIT

50436-019 130272 York, R. G., "Developmental toxicity study in New Zealand White rabbits", IRDC, Report # 672-002, 4/28/94. Creosote (P1/P13), Lot No. TOR-247552-3 (a composite mixture) was the "test article" administered to 20 female New Zealand White SPF rabbits per group at 0 (corn oil), 1, 9, and 75 mg/kg/day by gavage on gestation days 6 through 18. Maternal NOEL = developmental NOEL = 9 mg/kg/day (increased abortions, increased whole litter losses, and indications of reduced implantation efficiency). No adverse effects. The study is **acceptable, although several deficiencies are noted in the review. H. Green, C. Aldous, 1/10/95.

50436-017 115555, protocol for 130272.

GENE MUTATION

50436-012 55555, "Genotoxic Exposure of Workers Creosoting Wood" (Institute of Pharmacology, Toxicology Unit, University of Nijmegen, and the Occupational Health Service, Region Nijmegen, and the Occupational Health Service, Region Nijmegen, Nijmegen, The Netherlands, British Journal of Industrial Medicine 1984; 41:260-262). Creosote spill swab samples or ip-treated rat urine samples were tested for mutagenicity with Salmonella typhimurium strains TA98 and TA100 with or without S9 activation and with or without beta-glucuronidase treatment of urine samples. Commercial creosote (type P1, Cindu Chemicals BV, Uithoorn, The Netherlands) was reportedly markedly mutagenic in TA 98 and TA100 strains. Swab samples were reportedly mutagenic in TA98 (no report of testing with TA100). Rat urine samples appeared to have mutagenic components (increased revertants of both strains), the greatest numbers of reversions being in the presence of S9 mix plus beta-glucuronidase. Unacceptable, not upgradeable (Not a standard "Ames"-type mutagenicity study, incomplete report, but useful information). Green, C. Aldous, 7/8/87.

50436-021 132731 (Record No. 132731 is handwritten in text, but # listed in data base is 132721). Exact duplicate of Record No. 55555, above.

50436-021 132719 Record contains a letter from Vincent F. Simmon, Life Sciences Division, SRI, to Daniel C. Braun, Industrial Health Foundation, Pittsburgh, PA, followed by 6 pages of data. The data represent a gene mutation assay run with four strains of Salmonella typhimurium

and E. coli at concentrations of 0.01 ul/plate to 5.0 ul/plate, with and without activation, two trials. Both were negative for induction of reverse mutations. No protocol, no details. The materials tested were identified as Creosote P1 and Creosote P2. Unacceptable, upgradeability uncertain. No worksheet. Gee, 1/13/95.
[Note: 50436-018 contains a letter from John H. Butala, Duquesne University, to Eric Feris, Reregistration Branch, U.S. EPA, dated March 11, 1993, regarding genetic toxicity testing. This letter raises doubts about the early testing of complex mixtures, such as creosote, before the technology was well-developed.] See also comment under "Chromosome" below. Gee, 1/18/95.

50436-028 144578 "Mutagenicity of creosote in the Salmonella/microsome assay." (Bos, R. P., C. T. J. Hulshof, J. L. G. Theuws and P. Th. Henderson, Mutation Research 119: 21-25 (1983)) Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to creosote type P1 by plate incorporation at 0, 2, 5, 20 or 50 ug/plate with rat liver activation (no plates without activation). In addition, TA1537 was incubated with the epoxide hydratase inhibitor 1,2-epoxy-3,3,3-trichloropropane at 0, 2, 4, 8,16, 32, and 64 ug/plate with benzo(a)pyrene as the positive control. Mutagenic activity was demonstrated with 4 of the 5 strains with TA1535 being unresponsive. The presence of the epoxide hydratase inhibitor increased the mutagenic response. Unacceptable (no individual data, inadequate description of methods). Possibly upgradeable. **Possible adverse effect**. (Gee, 2/26/96)

Note: Although no one study meets the current guidelines, collectively the studies fill the data gap with a possible adverse effect noted in several studies. (Gee, 2/26/96)

CHROMOSOMAL EFFECTS

** 50436-027, -029 142480, 144623 "Rat dominant lethal testing of creosote P1/P13" (A. D. Mitchell, Genesys Research Incorporated, study number 94038, 9/25/95) Creosote P1/P13 composite (no lot number, no analytical data) was given by gavage on five consecutive days to male Sprague-Dawley rats, 20 per control and per low- and mid-dose groups, 25 in the high dose group. Doses were 0 (corn oil), 181.25, 362.5 or 725 mg/kg/day (analytical doses were 230.8, 330.5 and 857.5 mg/kg). They were mated for 10 weekly periods to two females (untreated) per male. Females were sacrificed and examined for corpora lutea and implantations. No further necropsy was performed. No evidence of a dominant lethal effect was noted. TEM as positive control. Unacceptable (no individual data), upgradeable. (Gee, 11/20/95) The requested individual data are in 029, 144623, upgrading the study to acceptable status. (Gee, 2/26/96)

50436-018 No record number. A letter dated March 11, 1993, from John H. Butala, Duquesne University, to Eric Feris, U.S. EPA, proposes that a rodent dominant lethal study using P1/P13 and P2 be conducted in place of an in vitro study. A list of results of 4 studies was included, summarizing overall results of individual tests as positive or negative using Creosotes P1 and P2. In general, both P1 and P2 were positive with Salmonella, L5178Y and a host-mediated assay, but P2 was negative with E. coli. Gee, 1/13/95. See 142480 above. Gee, 11/20/95.

DNA DAMAGE

Note: In a letter dated February 8, 1996, from John H. Butala representing the Creosote Council II, a waiver for this study type was requested. A memorandum was prepared March 18, 1996, by J. Gee to be sent to OEHHA through the Pesticide Registration Branch for concurrence. The registrants agree that creosote is mutagenic. J. Gee, 3/18/96. On 11/4/96, the staff of OEHHA concurred that no further testing for genotoxicity should be required for creosote at this time. Requirement for further testing is therefore waived by DPR at this time. Gee, 1/8/98.

50436-028 144577 Proposed methodology for a possible UDS study in primary rat hepatocytes (no DPR review: see above note).

NEUROTOXICITY

Not required at this time.

OTHER STUDY TYPES

A two-week inhalation exposure range-finding study has been completed, in preparation for a subchronic inhalation study of P2 creosote in rats. Exposure of 113 to 191 mg/m^3 led to brown discolorations of lungs and increased lung/trachea weights. Apparent NOEL was 15 mg/m^3. No data (information was part of a 2-page letter of 10/28/93). A related letter, dated 10/25/93, reported a comparable 2-week study using P1/P13 creosote. This study led to an apparent NOEL of 23 mg/m^3, based on increased liver weights. No DPR worksheet. Aldous, 1/11/95.

50436-023 136050 Butala, J. H. Two letters were submitted as "Adverse Health Effects Reports", each relating to 13-week rat inhalation toxicity studies in progress. The first was IRDC Study No. 671-018, employing "North American P2 Creosote". The second was IRDC Study No. 671-016, employing "North American P1/P13 Creosote". Each study used 20 rats/sex/group dosed 5 day/wk for 6 hr/day at exposure levels of 0, 5, 50, or 100 mg/m^3. Major findings common to both studies included: hematology changes, particularly depression of Hb and HCT, and reduced RBC counts; pigment deposition in lungs; squamous cell metaplasia and other changes in nasal epithelium; and thyroid hypertrophy or enlargement of thyroid epithelial cells. The second study found diffuse myocardial degeneration in 2 high dose and 1 mid-dose rat. Many of these changes persisted through a 6-wk recovery period. Aldous, July 6, 1995 (no data provided other than summaries in 2-page letters: no DPR review).

STUDIES APPEARING IN DATA BASE WHICH DO NOT RELATE TO SB-950 REQUIREMENTS

50436-016 113274 (Worker exposure data in wood pressure treatment plants)

180-016 54704 Data on petroleum waxes in support of other wood preservative products

50436-013 55834, 55836, 55837, and 55838 (studies on arsenicals)

50436-013 55886, 55887, and 55888 (studies on arsenicals)